Synthesis of Ethyl 2-(4-Chlorophenyl)-5-(2-furyl)-4-oxazoleacetate, a Hypolipidemic Agent, and Related Compounds[1]

Tamon Moriya,[†] Masahiko Seki,[†] Seiichi Takabe,[†] Kazuo Matsumoto,*[†] Kohki Takashima,[†] Tetsuji Mori,[‡] Akio Odawara,[‡] and Shigeyuki Takeyama[‡]

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 16-89, Kashima 3-Chome, Yodogawaku, Osaka 532, Japan, and Biological Research Laboratory, Tanabe Seiyaku Co., Ltd., 2-2-50, Kawaguchi, Toda, Saitama 335, Japan.
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A series of 2-aryl and 2-alkyl derivatives of 5-furyl-4-oxazoleacetic acid and their homologues having alkyl groups at the α-position of the acids were synthesized and evaluated for their hypolipidemic activities in Sprague–Dawley rats. On the basis of the structure–activity relationships and subacute toxicities, ethyl 2-(4-chlorophenyl)-5-(2-furyl)-4-oxazoleacetate (**35**) was selected as a candidate compound for development. Compound **35** reduced serum cholesterol and triglyceride levels by 23% and 35%, respectively, at a dose of 0.05% in a diet in normal rats, and it was about 10 times more active in hereditary hyperlipidemic rats (THLR/1) than in normal rats. Compound **35** inhibited platelet aggregation in vitro and also normalized hyperaggregability of hyperlipidemic plasma platelet ex vivo.

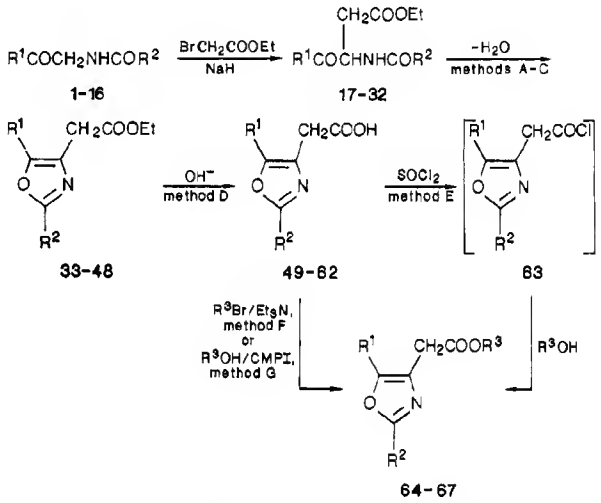
It is widely accepted that elevated plasma cholesterol levels lead to premature artheriosclerosis[2] and consistute one of the most important risk factors for the increased incidence of coronary heart disease.[3] Much attention has been paid to the development of a more satisfactory hypolipidemic agent such as an agent effective for Type IIa[4] hyperlipidemia. In our previous work[5] as a part of development of new drugs from α-amino acids, we reported synthesis and structure–hypolipidemic activity relationships of 2,4,5-trisubstituted oxazole derivatives and found that a series of 2-aryl-5-thienyl-4-oxazoleacetic acid derivatives exerted potent hypocholesterolemic and hypotriglyceridemic activities.

The present study deals with further structural modification of the 2-aryl-4-oxazoleacetic acids having a furyl group instead of the thienyl group at C-5 on the oxazole ring. In addition, 2-alkyl-4-oxazoleacetic acids with a thienyl or furyl group at C-5 were also evaluated. Among these derivatives, ethyl 2-(4-chlorophenyl)-5-(2-furyl)-4-oxazoleacetate (**35**) was selected as the most promising candidate with more potent hypocholesterolemic and hypotriglyceridemic activities than clofibrate [ethyl 2-(*p*-chlorophenoxy)isobutyrate] in normal and hereditary hyperlipidemic rats.

Chemistry

A series of ethyl 2,5-disubstituted-4-oxazoleacetates (**33–48**) were synthesized according to the previously reported method[5] as shown in Scheme I. For the preparation of an intermediate, 3-(4-chlorobenzamido)-3-furoylpropionate (**19**), the Dakin–West reaction[6] with aspartic acid azlactone (**68**) and furoyl chloride, was also applied. For the cyclization of β-(acylamino)-γ-keto ester (**21** and **25**), thionyl chloride (method B) and phosphorus pentoxide (method C) were also useful as dehydrating agents instead of phosphoryl chloride (method A) reported previously.[5] The ethyl oxazoleacetates (**33–40**, **42**, and **44–48**) formed were saponified in aqueous methanol (method D) to afford the corresponding acids (**49–62**). Esterification of the oxazoleacetic acid (**51**) to higher esters (**64–67**) was carried out by the following three methods: (E) conversion to the corresponding acid chloride (**63**) with thionyl chloride followed by reaction with an alcohol, (F) direct alkylation of the acid with an alkyl halide in the presence of triethylamine, and (G) direct condensation of the acid (**51**) with an alcohol with use of 2-chloro-1-methylpyridinium iodide (CMPI) as a condensation agent.

Scheme I



The α-alkyl homologues (**69–72**) of ethyl 5-furyl-4-oxazoleacetates (**35** and **45**) were easily prepared by mono- and di-α-alkylation on the active methylene group of the oxazoleacetic acid moiety with use of usual metallic bases such as sodium hydride as illustrated in Scheme II. The esters obtained were hydrolyzed to the corresponding acids (**73** and **74**).

Introduction of substituents to C-5 on the furyl ring of compound **35** was performed by electrophilic substitution reactions (method H) with Vilsmeier–Haack reagents for the formyl group (compound **75**), Friedel–Crafts reagents for the acetyl group (compound **76**), bromine for the bromo group (compound **77**), and sulfuric acid for the sulfo group (compound **78**). Catalytic hydrogenation of the furyl group of compound **35** to a tetrahydrofuryl derivative accompanied elimination of chlorine on the phenyl group to yield

[†] Research Laboratory of Applied Biochemistry.
[‡] Biological Research Laboratory.

(1) Synthesis of Amino Acids and Related Compounds. 34. Part 33: Seki, M.; Moriya, T.; Matsumoto, K. *Agric. Biol. Chem.* **1987**, *51*, 3033.
(2) Dresel, H. A.; Friedrich, E. A.; Otto, I.; Waldherr, R. Schettler, G. *Arzneim.-Forsch.* **1985**, *35*, 1936.
(3) Report of LRC-CPPT (Lipid Research Clinics Coronary Primary Prevention Trial); *J. Am. Med. Assoc.* **1984**, *251*, 351.
(4) Beaumont, J. L.; Carlson, L. A.; Cooper, G. R.; et al. *Bull. W.H.O.* **1970**, *43*, 891.
(5) Moriya, T.; Takabe, S.; Maeda, S.; Matsumoto, K.; Takashima, K.; Mori, T.; Takeyama, S. *J. Med. Chem.* **1986**, *29*, 333.
(6) Seki, M.; Kubota, H.; Moriya, T.; Yamagishi, M.; Nishimoto, S.; Matsumoto, K. *Chem. Pharm. Bull.* **1986**, *34*, 4516.

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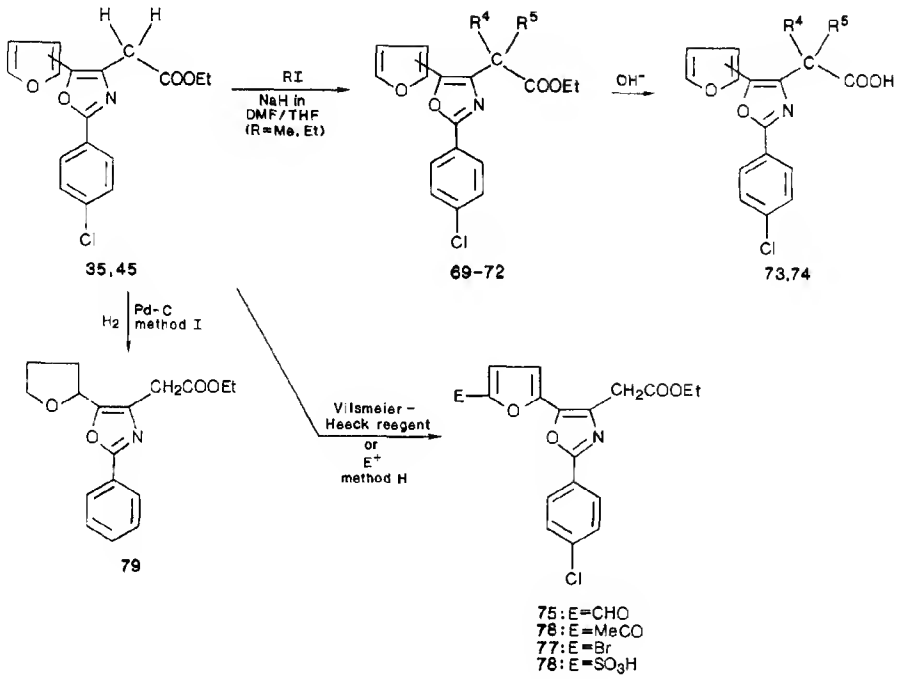
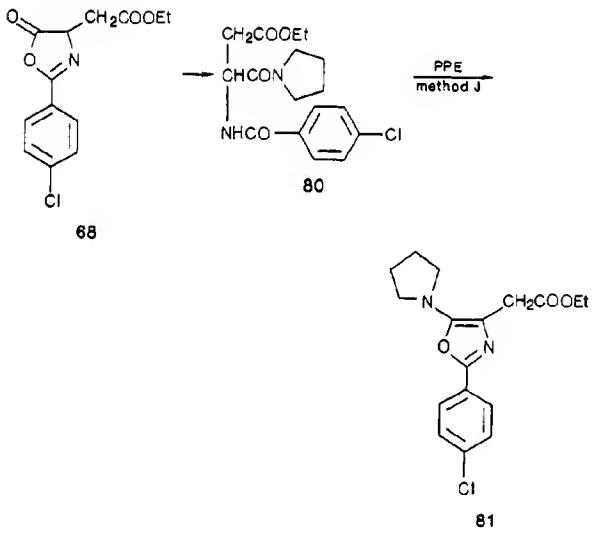
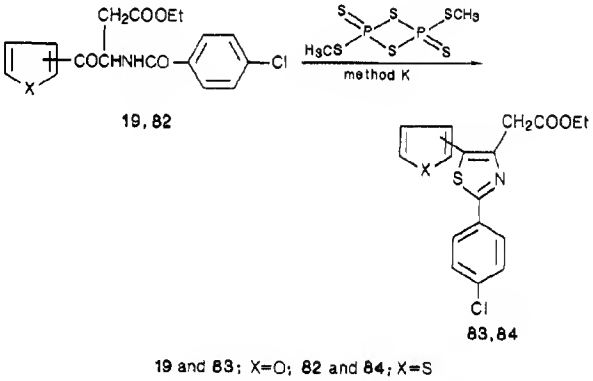
Scheme II



Scheme III



Scheme IV



compound **79** (method I, Scheme II).

A derivative (**81**) having a 1-pyrrolidinyl group on C-5 of the oxazole ring was synthesized from the aspartic acid diamide β-ester (**80**), which was prepared from aspartic acid azlactone (**68**) and pyrrolidine: **80** was cyclized by polyphosphoric acid ethyl ester (PPE) to afford the desired **81** in good yield (method J, Scheme III).

For syntheses of ethyl 5-furyl- and 5-thienyl-4-thiazoleacetates (**83** and **84**), the β-(acylamino)-γ-ketobutyrates (**19** and **82**[5]) were treated with 2,4-bis(methylthio)-2,4-dithioxo-1,3,2,4-dithia di-2λ⁵,4λ⁵-phosphetate (BMDDP),[10] which introduced a sulfur atom to the amide group and then cyclized the resulting thioamide to the desired thiazole ring simultaneously in good yield (method K, Scheme IV).

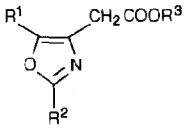
Biological Results and Discussion

Hypolipidemic activities of all test compounds were evaluated by the same way as described in the previous report[5] with male Sprague–Dawley (SD) rats. The activities were expressed as percent decreases in serum cholesterol and triglycerides in comparison to control animals after 7-day dosing at 0.05% in a diet. Under the same conditions, the positive control drug, clofibrate, reduced serum cholesterol and triglyceride by 15% and 30%, respectively. Since serum triglyceride levels in the rat were more variable than cholesterol levels, more emphasis was placed on hypocholesterolemic activities rather than hypotriglyceridemic ones in assessing the hypolipidemic activity of test compounds.

In the foregoing paper, we reported that the acetic acid group at C-4 and the thienyl group at C-5 were both essential substituents on the oxazole ring for hypolipidemic activity. Consequently, 2-(4-fluorophenyl)-5-(3-thienyl)-4-oxazoleacetic acid (**85**), which reduced serum cholesterol and triglyceride by 23% and 39%, respectively, was selected from the series of 2-aryl-5-thienyl-4-oxazoleacetic acid derivatives as the most hopeful compound.[5]

To clarify further structure–activity relationships and to obtain more effective agents, the thienyl group at C-5 of compound (**85**) analogues was replaced for a furyl group. As a result, a similar structure–activity relationship to that of the earlier thienyl congeners was formulated, and some of the furyl derivatives showed higher hypolipidemic activities than the thienyl series.

Table I. Physicochemical Properties and Hypolipidemic Activities of Ethyl 4-Oxazoleacetates and the Acids

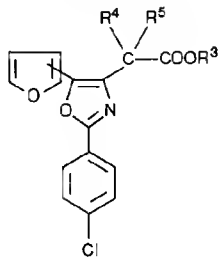


compd	R^1	R^2	R^3	method[a]	yield,[b] %	mp, °C	IR,[c] cm^{-1} $\nu_{C=O}$	formula[d]	reduction[e] Cho	reduction[e] TG	inhibn of platelet aggregation[f]
33	2-furyl	Ph	Et	A	79	79–80	1735	$C_{17}H_{15}NO_4$	14	23	+
34	2-furyl	4-FPh	Et	A	80	110–111	1725	$C_{17}H_{14}NO_4F$	20[g]	24[g]	+
35	2-furyl	4-ClPh	Et	A	86	107–108	1723	$C_{17}H_{14}NO_4Cl$	23[g]	35[g]	+
36	2-furyl	4-MePh	Et	A	42	84–85	1725	$C_{18}H_{17}NO_4$	9	−6	+
37	2-furyl	4-MeOPh	Et	B	32	64–66	1730	$C_{18}H_{17}NO_5$	0	4	+
38	2-furyl	3-CF_3Ph	Et	A	93	101–102	1735	$C_{18}H_{14}NO_4F_3$	15	0	−
39	2-furyl	Me	Et	A	80	syrup	1735[h]	$C_{12}H_{13}NO_4$	*	*	*
40	2-furyl	*i*-Pr	Et	A	89	syrup	1735[h]	$C_{14}H_{17}NO_4$	12[g]	21	−
41	2-furyl	*n*-Bu	Et	C	85	syrup	1735[h]	$C_{15}H_{19}NO_4$	2	16	++
42	2-furyl	c-C_6H_{11}	Et	A	70	syrup	1740[h]	$C_{17}H_{21}NO_44$	*	*	*
43	3-furyl	Ph	Et	A	75	84–85	1718	$C_{17}H_{15}NO_4$	17	46[g]	+
44	3-furyl	4-FPh	Et	A	66	102–103	1720	$C_{17}H_{14}NO_4F$	30[g]	28[g]	+
45	3-furyl	4-ClPh	Et	A	86	124–125	1725	$C_{17}H_{14}NO_4Cl$	25[g]	42[g]	+
46	3-furyl	3,4-Cl_2Ph	Et	A	47	130–131	1730	$C_{17}H_{13}NO_4Cl_2$	19[g]	49[g]	−
47	3-thienyl	*i*-Pr	Et	A	63	syrup	1740[h]	$C_{14}H_{17}NO_3S$	15	28	+
48	3-thienyl	*n*-C_7H_{15}	Et	A	80	syrup	1735[h]	$C_{18}H_{25}NO_3S$	*	*	*
49	2-furyl	Ph	H	D	78	175–177	1690	$C_{15}H_{11}NO_4$	14[g]	29[g]	+
50	2-furyl	4-FPh	H	D	88	212–214	1700	$C_{15}H_{10}NO_4F$	20[g]	10	+
51	2-furyl	4-ClPh	H	D	91	191–194	1720	$C_{15}H_{10}NO_4Cl$	20[g]	35[g]	+
52	2-furyl	4-MePh	H	D	56	176–177	1720	$C_{16}H_{13}NO_4$	9	29[g]	+
53	2-furyl	4-MeOPh	H	D	82	177–178	1700	$C_{16}H_{13}NO_5$	5	−1	+
54	2-furyl	3-CF_3Ph	H	D	76	210–221	1690	$C_{16}H_{10}NO_4F_3$	8	50[g]	+
55	2-furyl	Me	H	D	57	103–104	1720	$C_{10}H_9NO_4$	10	−20	−
56	2-furyl	*i*-Pr	H	D	67	108–109	1730	$C_{12}H_{13}NO_4$	5	9	−
57	2-furyl	c-C_6H_{11}	H	D	80	99–100	1730	$C_{15}H_{17}NO_4$	13	18	+
58	3-furyl	4-FPh	H	D	85	208–209	1710	$C_{15}H_{10}NO_4F$	23[g]	38[g]	+
59	3-furyl	4-ClPh	H	D	88	218–219	1715	$C_{15}H_{10}NO_4Cl$	23[g]	42[g]	++
60	3-furyl	3,4-Cl_2Ph	H	D	81	222–223	1725	$C_{15}H_9NO_4Cl_2$	19	60[g]	+
61	3-thienyl	*i*-Pr	H	D	60	118–119	1725	$C_{12}H_{13}NO_3S$	20[g]	16	+
62	3-thienyl	*n*-C_7H_{15}	H	D	68	63–64	1720	$C_{18}H_{21}NO_3S$	11	27	+
64	2-furyl	4-ClPh	*n*-C_7H_{15}	E	43	69–70	1735	$C_{22}H_{24}NO_4Cl$	19[g]	42[g]	−
65	2-furyl	4-ClPh	*n*-Bu	F	62	96–97	1730	$C_{19}H_{18}NO_4Cl$	20[g]	27	−
66	2-furyl	4-ClPh	*n*-$C_{12}H_{25}$	G	77	70–71	1730	$C_{27}H_{34}NO_4Cl$	20[g]	30	−
67	2-furyl	4-ClPh	3-picolyl	G	47	133–134	1730	$C_{21}H_{15}N_2O_4Cl$	18[g]	42[g]	−
75	5-CHO-2-furyl	4-ClPh	Et	H	49	139–140	1710	$C_{18}H_{14}NO_5Cl$	9	−5	*
76	5-CH_3CO-2-furyl	4-ClPh	Et	H	47	151–152	1730	$C_{19}H_{16}NO_5Cl$	0	−14	*
77	5-Br-2-furyl	4-ClPh	Et	H	66	120–121	1720	$C_{17}H_{13}NO_4BrCl$	10	2	*
78	5-SO_3H-2-furyl	4-ClPh	Et	H	41	186–187	1730	$C_{17}H_{14}NO_7SCl$	−5	23	*
79	2-tetrahydrofuryl	Ph	Et	I	34	syrup	1740	$C_{17}H_{19}NO_4$	8	8	−
81	1-pyrrolidinyl	4-ClPh	Et	J	95	103–104	1730	$C_{17}H_{19}N_2O_3Cl$	−2	−20	*
83[i]	2-furyl	4-ClPh	Et	K	85	94–95	1725	$C_{17}H_{14}NO_3SCl$	−15	17	*
84[i]	3-thienyl	4-ClPh	Et	K	quant	67–68	1735	$C_{17}H_{14}NO_2S_2Cl$	−8	21	*
85[5]	3-thienyl	4-ClPh	Et						23[g]	39[g]	+
clofibrate									15 ± 1[j]	30 ± 2[j]	−
aspirin									*	*	++

[a] A: Dehydrative cyclization with phosphoryl chloride. B: Dehydrative cyclization with thionyl chloride. C: Dehydrative cyclization with phosphorus pentoxide. D: Saponification with potassium hydroxide. E: Direct alkylation of the acid with alkylhalide in the presence of triethylamine. F: Esterification via acid chloride. G: Esterification with CMPI and triethylamine. H: Electrophilic substitution on the furyl group of **35**. I: Hydrogenation of **35** with palladium–carbon catalyst. J: Dehydrative cyclization of **80** with PPE. K: Simultaneous thioamidation and dehydrative cyclization by BMDDP. [b] Yields of the ethyl oxazoleacetates **33–48**, the oxazoleacetic acids **49–62**, the compounds **75–79**, the esters **64–67**, and the compounds **81**, **83**, and **84** were calculated on the basis of the corresponding acylamino ketones **17–32**, ethyl oxazoleacetates **33–40**, **42**, and **44–48**, oxazoleaceate **35**, oxazoleacetic acid **51**, and compounds **80**, **19**, and **82**, respectively. [c] Measured as a Nujol mull. [d] All compounds were analyzed for C, H, N, F, Cl, and S, and the results were within ±0.4% of theory. [e] Male SD rats. Dosing at 0.05% in a diet. Asterisks signify no evaluation. [f] In vitro data (100 μg/mL); (+) indicates ≥10% but < aspirin (34–96%); (++) indicates inhibition ≥ aspirin (see the Experimental Section). [g] Statistically significant depression with $p < 0.05$ by the Student's *t* test. [h] Measured as a film. [i] 4-Thiazoleacetate. [j] Means ±SE ($N = 33$).

Namely, the substituents having electron-withdrawing effects on the phenyl group at C-2 of the oxazole ring caused lowering of serum cholesterol levels, whereas the substituents with electron-donating properties were ineffective. For example, compounds bearing a halogen atom showed higher hypocholesterolemic activities than those having a methyl or methoxy group (compare compounds **34**, **35**, **50**, and **51** with **36**, **37**, **52**, and **53** in Table I). Concerning the furyl group on C-5 of the oxazole ring, 3-furyl derivatives showed activities similar to or somewhat higher than those of 2-furyl analogues (compare compounds **34**, **35**, **50**, and **51** with **44**, **45**, **58**, and **59**, respectively, in Table I). Introduction of substituents to the furyl group was detrimental (see compounds **75–78**). Exchange of the ethyl ester group of compound **35** for higher alkyl ester groups having up to 12 carbon atoms or a pyridylmethyl ester group scarcely affected the activity; i.e., they exhibited approximately the same or less degrees of re-

Table II. Preparation and Hypolipidemic Activities of Ethyl 4-(Chlorophenyl)-5-furyl-4-oxazolealkanoates and the Acids



compd	furyl	R^3	R^4	R^5	yield,[a] %	mp, °C	IR,[b] cm^{-1} $\nu_{C=O}$	formula[c]	reduction,[d] % Cho	reduction,[d] % TG	inhibition of platelet aggregation[e]
69	2-furyl	Et	H	Me	88	97–98	1740	$C_{18}H_{16}NO_4Cl$	20[f]	31	+
70	3-furyl	Et	H	Me	73	108–109	1735	$C_{18}H_{16}NO_4Cl$	22[f]	45[f]	+
71	2-furyl	Et	H	Et	47	55–56	1725	$C_{19}H_{18}NO_4Cl$	0	-10	-
72	2-furyl	Et	Me	Me	84	89–90	1730	$C_{19}H_{18}NO_4Cl$	-4	-25	-
73	2-furyl	H	H	Me	64	186–187	1710	$C_{16}H_{12}NO_4Cl$	16	41	*
74	2-furyl	H	Me	Me	86	186–189	1720	$C_{17}H_{14}NO_4Cl$	16	54[f]	-

[a] Yields were based on the oxazoleacetates **35** and **45** and oxazolepropionates **69** and **72**. [b] Measured as a Nujol mull. [c] All compounds were analyzed for C, H, N, F, Cl, and S, and the results were within ±0.4% of theory. [d] Male SD rats. Dosing at 0.05% in a diet. Asterisks signify no evaluation. [e] In vitro data (100 mg/mL); (+) indicates ≥10% but < aspirin (34–96%); (++) indicates inhibition ≥ aspirin (see the Experimental Section). Asterisks signify no evaluation. [f] Statistically significant depression with $p < 0.05$ by the Student's t test.

duction in serum lipids (see compounds **64–67**).

Among the 2-aryl-5-furyl-4-oxazoleacetic acid analogues, compounds (**35** and **45**) having a 2-furyl or 3-furyl moiety on C-5 of ethyl 2-(4-chlorophenyl)-4-oxazoleacetate were the most effective: compound **35** reduced serum cholesterol and triglyceride by 23% and 35%, respectively, and compound **45** reduced the lipid levels by 25% and 42%, respectively.

To further investigate effects of the substituent at C-2 on the oxazole ring, we synthesized 2-alkyl derivatives of 4-oxazoleacetates having a furyl or thienyl group on C-5. These compounds (**40**, **47**, **57**, **61**, and **62** in Table I) showed moderate to high activities. For instance, 2-isopropyl-5-(3-thienyl)-4-oxazoleacetic acid (**61**) reduced serum cholesterol and triglyceride by 20% and 16%, respectively.

Generally, however, this series was slightly less active than the former 2-aryl series.

To examine the indispensable substituent on C-5 of the 4-oxazoleacetic acid, the furyl group was converted to a saturated heterocyclic group. The tetrahydrofuryl compound (**79**) showed only weak hypocholesterolemic and hypotriglyceridemic activities. Another derivative (**81**) having a 1-pyrrolidinyl group elevated the levels of cholesterol and triglycerides by 2% and 20%, respectively. Therefore, a heteroaromatic group such as a furyl or thienyl group on C-5 of the oxazole ring seems to be a necessary substituent.

Concerning the substituent at C-4 on the oxazole, it was reported[5] that the acetic acid group was the most favorable group among the acid groups having one to three carbon atoms in 5-thienyloxazole derivatives. In the 5-furyloxazole series, analogues having a propionic acid moiety prepared by introduction of a methyl group to the α-position of the acetic acid group showed reductions of serum lipids similar to those by original acetic acid derivatives (compare compounds **35**, **45**, and **51** with **69**, **70**, and **73**, respectively, in Tables I and II). α-Methyl-α-[2-(4-chlorophenyl)-5-(2-furyl)-4-oxazolyl]propionic acid (**74**), which was prepared by further introduction of a methyl group to the α-position of the foregoing propionic acid derivative (**69**) followed by hydrolysis, reduced serum cholesterol and triglycerides by 16% and 54%, respectively. On the other hand, introduction of an ethyl group significantly decreased the hypolipidemic activity (see compound **71** in Table II).

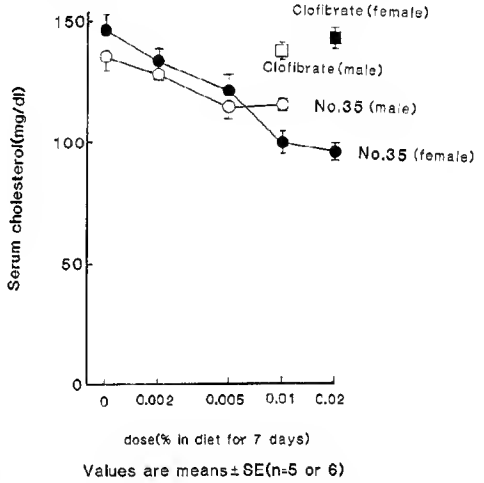


Figure 1. Hypocholesterolemic effect of **35** in THLR (Tanabe hyperlipidemic rats).

Furthermore, the oxazole ring was replaced for an analogous thiazole ring to study the structure–activity relationship. Interestingly thiazoleacetates (**83** and **84**), corresponding to original oxazoleacetates (**35** and **85**), showed only weak hypotriglyceridemic activities and increased the cholesterol level by 15% and 8%, respectively. Thus, the indispensability of the oxazole ring is apparent in these results.

Thus, on the basis of the above data and some other pharmaceutical considerations that will be reported elsewhere,[7] we selected compound **35** as a candidate compound for development. In Tanabe hyperlipidemic rats (THLR),[8] a model of hereditary hyperlipidemia developed in our laboratory, **35** exhibited a higher activity than in normals rats. As shown in Figure 1, **35** lowered the serum cholesterol level dose dependently. In male hyperlipidemic rats, the percent decreases after administration of **35** at doses of 0%, 0.002%, 0.005%, and 0.01% (0.01% in the diet

(7) To be published elsewhere.
(8) Fujinami, F.; Mori, T.; Takashima, K.; Ohshima, S. Japanese Association for Laboratory Animal Science 18th Meeting, Kobe, 1984, Abstract A-65.

Table III. (*N*-Acylamino)methyl Ketones

$R^1COCH_2NHCOR^2$

compd	R^1	R^2	yield,[a] %	mp, °C	IR,[b] cm^{-1} ν_{NH}	IR,[b] cm^{-1} $\nu_{C=O}$ ketone	IR,[b] cm^{-1} $\nu_{C=O}$ amide
1	2-furyl	Ph	83	132–133	3400	1675	1600
2	2-furyl	4-FPh	67	152–155	3410	1685	1655
3	2-furyl	4-ClPh	98	138–139	3300	1680	1660
4	2-furyl	4-MePh	83	139–141	3300	1690	1635
5	2-furyl	4-MeOPh	85	114–115	3310	1690	1635
6	2-furyl	3-CF_3Ph	95	123–124	3370	1675	1640
7	2-furyl	Me	45	114–115	3380	1670	1655
8	2-furyl	*i*-Pr	67	78–80	3300	1680	1655
9	2-furyl	*n*-Bu	77	64–65	3320	1690	1630
10	2-furyl	c-C_6H_{11}	92	110–111	3250	1690	1630
11	3-furyl	Ph	92	102–103	3400	1680	1645
12	3-furyl	4-FPh	93	142–143	3370	1670	1640
13	3-furyl	4-ClPh	quant	152–154	3350	1675	1635
14	3-furyl	3,4-Cl_2Ph	82	133–134	3460	1680	1650
15	3-thienyl	*i*-Pr	76	100–101	3250	1685	1625
16	3-thienyl	*n*-C_7H_{15}	90	87–88	3370	1685	1640

[a] Yields were based on the corresponding aminomethyl heteroaryl ketone hydrochlorides.[5] [b] Measured as a Nujol mull.

corresponded to about 4.4 mg/kg per day) were 2%, 3%, 13%, and 14%, respectively. On the other hand, clofibrate at a dose of 0.01% did not show such an effect. In female hyperlipidemic rats, **35** at doses of 0%, 0.002%, 0.005%, 0.01%, and 0.02% (0.02% in the diet corresponded to about 9.6 mg/kg per day) also lowered serum cholesterol by 2%, 7%, 14%, 30%, and 33%, respectively, while clofibrate did not exert the activity even at a dose of 0.02%. Concerning the serum triglyceride level, **35** lowered it at doses higher than 0.005%, whereas clofibrate did not influence it at these doses.

Additionally, **35** and the deesterified compound **51** inhibited platelet aggregation in vitro by 28% and 24%, respectively, at a concentration of 100 μg/mL. When **35** was orally administered to rats on a cholesterol-rich diet at a dose of 100 mg/kg per day for 2 weeks, the hyperaggrigability of hyperlipidemic plasma platelet was normalized by 75%.

The oral LD_{50} of **35** in both male and female rats was above 2000 mg/kg. After 3 months of dosing at 2000 mg/kg in the diet, there were neither significant changes in body weight nor increase in the liver weight, unlike with clofibrate.[7,9]

Experimental Section

Chemistry. Melting points were measured by the use of a Yamato melting point apparatus and are uncorrected. The IR spectra were obtained on a Shimadzu IR-27G infrared spectrophotometer. The ^1H NMR spectra were recorded on a Hitachi-Perkin-Elmer R-20A high-resolution NMR spectrometer with tetramethylsilane as an internal standard. The mass spectra were taken on a Hitachi RMU-6M spectrometer at an ionizing potential of 30 eV. Column chromatography was carried out on silica gel (Kiesel gel 60, 0.063–0.200 mm, E. Merck).

Materials. (Acylamino)methyl heteroaryl ketones (**1–16**) were prepared by acylation of the corresponding aminomethyl heteroaryl ketone hydrochlorides according to the previous method.[5] Aminomethyl 3-furyl ketone hydrochloride was prepared as follows. Methyl 5-(3-furyl)oxazole-4-carboxylate [mp 87–88 °C; IR (Nujol) 3120, 1695 cm^{-1}; NMR ($CDCl_3$) δ 3.97 (3 H, s), 6.96 (1 H, d, J = 2 Hz), 7.47 (1 H, t, J = 2 Hz), 7.80 (1 H, s), 8.49 (1 H, d, J = 2 Hz)] was synthesized from methyl α-isocyanoacetate and 3-furoyl chloride. The oxazole-4-carboxyate was converted by hydrolysis with hydrochloric acid to aminomethyl 3-furyl ketone hydrochloride, which was characterized by the following spectral data: mp 196–198 °C dec; IR (Nujol) 3110, 1650, 1560 cm^{-1}; NMR (Me_2SO-d_6) δ 4.31 (2 H, s), 6.84 (1 H, d, J = 2 Hz), 7.85 (1 H, t, J = 2 Hz), 8.22–9.12 (3 H, m), 8.38 (1 H, br d, J = 2 Hz).

Typical Procedure for the Syntheses of (*N*-Acylamino)methyl Ketones (1-16). [*N*-(4-Chlorobenzoyl)amino]methyl 3-Furyl Ketone (13). To a mixture of an aqueous solution of aminomethyl 3-furyl ketone hydrochloride (16.2 g, 0.1 mol) in H_2O (100 mL) and EtOAc (400 mL) were added $NaHCO_3$ (18.5 g, 0.22 mol) and subsequently, 4-chlorobenzoyl chloride (19.3 g, 0.11 mol) dropwise at 0 °C with vigorous stirring. After the stirring was continued overnight at room temperature, the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was crystallized from a small amount of EtOAc to afford colorless needles of **13** (27.0 g, quant): mp 152–154 °C; IR (Nujol) 3350, 3110, 1675, 1635, 1595 cm^{-1}; NMR ($CDCl_3$ and Me_2SO-d_6) δ 4.53 (2 H, d, J = 6 Hz), 6.21 (1 H, d, J = 2 Hz), 7.33 and 7.82 (2 H each, $A_2'B_2'$, J = 8 Hz), 7.47 (1 H, t, J = 2 Hz), 8.28 (1 H, d, J = 2 Hz), 8.48 (1 H, br t, J = 6 Hz); MS, m/z 263 and 265 (M^+).

In a similar manner, other (*N*-acylamino)methyl ketones (**1–12** and **14–16**) were synthesized from the corresponding aminomethyl heteroaryl ketone hydrochlorides. The yields and physicochemical data are listed in Table III.

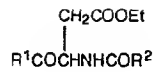
Typical Procedure for the Introduction of an (Ethoxycarbonyl)methyl Group to the (*N*-Acylamino)methyl Ketones (1–16). Ethyl 3-[*N*-(4-Chlorobenzoyl)amino]-4-(3-furyl)-4-oxobutyrate (29). Sodium hydride dispersion (60% on paraffine, 4.0 g, 0.1 mol) was added portionwise to a solution of **13** (21.5 g, 0.08 mol) in *N*,*N*-dimethylformamide (DMF, 150 mL) at −40 to −50 °C with stirring. The mixture was stirred for 20 min, and then ethyl bromoacetate (15.1 g, 0.09 mol) was added dropwise at the same temperature. After the temperature was allowed to rise to 10 °C within 30 min, the reaction was quenched with acetic acid (2 mL). The mixture was poured into H_2O (500 mL) and extracted with EtOAc (300 mL × 2). The extracts were combined, washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, and then concentrated. The residue was triturated with EtOH to afford colorless prisms of **29** (21.53 g, 77%): mp 93–95 °C; IR (Nujol) 3340, 3100, 1705, 1670, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (3 H, t, J = 8 Hz), 2.88 (2 H, d, J = 6 Hz), 4.14 (2 H, q, J = 7 Hz), 5.55 (1 H, m), 6.75 (1 H, d, J = 2 Hz), 7.32 and 7.69 (2 H each, $A_2'B_2'$, J = 9 Hz), 7.18–8.00 (2 H, m), 8.23 (1 H, d, J = 2 Hz); MS, m/z 349 (M^+).

Introduction of (ethoxycarbonyl)methyl group to other (*N*-acylamino)methyl ketones (**1–12** and **14–16**) was similarly carried out to afford the corresponding 3-[(*N*-acylamino)methyl]-4-oxobutyrates (**17–28** and **30–32**), and the yields and physicochemical data are summarized in Table IV.

Typical Procedure for the Cyclization of Ethyl 3-(*N*-Acylamino)-4-oxobutyrates (17–32) to Ethyl 4-Oxazole-

(9) Hess, R.; Staublei, W.; Riess, W. *Nature (London)* **1965**, *208*, 856.

Table IV. Ethyl 3-(Acylamino)-4-oxobutyrates



compd	R^1	R^2	yield,[a] %	mp, °C	IR,[b] cm^{-1} ν_{NH}	$\nu_{C=O}$ ester	$\nu_{C=O}$ ketone	$\nu_{C=O}$ amide
17	2-furyl	Ph	73	75–56	3300	1715	1680	1640
18	2-furyl	4-FPh	65	96–97	3300	1725	1690	1640
19	2-furyl	4-ClPh	70	100–102	3300	1738	1680	1630
20	2-furyl	4-MePh	86	84–85	3300	1715	1680	1635
21	2-furyl	4-MeOPh	73	104–106	3300	1715	1680	1635
22	2-furyl	3-CF_3Ph	80	72–73	3130	1715	1680	1635
23	2-furyl	Me	41	82–84	3280	1735	1680	1650
24	2-furyl	*i*-Pr	64	65–67	3270	1730	1660	1650
25	2-furyl	*n*-Bu	70	50–51	3280	1735	1675	1640
26	2-furyl	c-C_6H_{11}	56	58–60	3330	1725	1680	1640
27	3-furyl	Ph	86	108–110	3290	1725	1670	1635
28	3-furyl	4-FPh	70	107–109	3290	1725	1670	1640
29	3-furyl	4-ClPh	77	93–95	3340	1705	1670	1640
30	3-furyl	3,4-Cl_2Ph	92	127–129	3330	1715	1690	1640
31	3-thienyl	*i*-Pr	79	syrup	3330[c]	1730[c]	1660[c]	
32	3-thienyl	*n*-C_7H_{15}	58	47–49	3300	1730	1670	

[a] Yields were based on the (acylamino)methyl ketones. [b] Measured as a Nujol mull. [c] Measured as a film.

acetates (33–48). Ethyl 2-(4-Chlorophenyl)-5-(2-furyl)-4-oxazoleacetate (35). Method A. To a solution of **19** (35.0 g, 0.1 mol) in DMF (100 mL) was added dropwise phosphoryl chloride (18.5 g, 0.12 mol) at −5 °C, and the whole mixture was stirred for 8 h at ambient temperature. The reaction mixture was poured into a mixture of ice–water (500 mL) and EtOAc (500 mL) and neutralized with $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was crystallized from EtOH to obtain colorless needles of the oxazoleacetate **35** (28.5 g, 86%): mp 107–108 °C; IR (Nujol) 1725, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (3 H, t, J = 7 Hz), 4.00 (2 H, s), 4.29 (2 H, q, J = 7 Hz), 6.55–6.70 (1 H, m), 6.82 (1 H, d, J = 5 Hz), 7.35–7.77 (1 H, m), 7.55 and 8.15 (2 H each, $A_2'B_2'$, J = 8 Hz); MS, m/z 331 and 333 (M^+).

In a similar manner, dehydrative cyclization of the other butyrates (**17**, **18**, **20**, **22–24**, and **26–32**) were performed to give the corresponding oxazoleacetates (**33**, **34**, **36**, **38–40**, and **42–48**). The yields and physicochemical data are shown in Table I.

Ethyl 5-(2-Furyl)-2-(4-methoxyphenyl)-4-oxazoleacetate (37). Method B. A mixture of **21** (3.45 g, 0.01 mol), thionyl chloride (3.57 g, 0.03 mol), and a few drops of pyridine in $CHCl_3$ (50 mL) was refluxed for 6 h. The reaction mixture was poured into a mixture of ice and saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with $CHCl_3$ (100 mL), and the combined organic parts were dried over anhydrous $MgSO_4$. After concentration, the crude products were purified on a SiO_2 column with a mixed solvent of *n*-hexane and EtOAc (5:1) as an eluent to afford **37** (1.05 g, 32%) as colorless needles from EtOH: mp 64–66 °C; IR (Nujol) 3130, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 3.87 (3 H, s), 3.88 (2 H, s), 4.16 (2 H, q, J = 7 Hz), 6.44 (1 H, dd, J = 2 and 4 Hz), 6.61 (1 H, d, J = 4 Hz), 6.90 and 7.95 (2 H each, $A_2'B_2'$, J = 8 Hz), 7.44 (1 H, br s); MS, m/z 327 (M^+).

Ethyl 5-Butyl-2-(2-furyl)-4-oxazoleacetate (41). Method C. Phosphorus pentoxide (10 g, 0.065 mol) was added to a suspension of **25** (2.95 g, 0.01 mol) and diatomaceous earth (10 g) in dry CH_2Cl_2 (50 mL) with vigorous stirring, and the whole mixture was refluxed for 10 h. The CH_2Cl_2 layer was decanted and washed with saturated aqueous $NaHCO_3$ solution. After being dried over anhydrous $MgSO_4$, the CH_2Cl_2 layer was concentrated and chromatographed on a SiO_2 column with a mixed solvent of *n*-hexane and EtOAc (5:1) to afford **41** (2.35 g, 85%) as colorless syrup: IR (film) 3130, 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (3 H, t, J = 6 Hz), 1.22 (3 H, t, J = 7 Hz), 0.8–2.10 (4 H, m), 2.77 (2 H, t, J = 6.5 Hz), 3.78 (2 H, s), 4.17 (2 H, q, J = 7 Hz), 6.40 (1 H, dd, J = 2 and 4 Hz), 6.53 (1 H, d, J = 4 Hz), 7.40 (1 H, br s); MS, m/z 277 (M^+).

Typical Procedure for the Saponification of the 4-Oxazoleacetates (33–40, 42, and 44–48) to the Acids (49–62). 2-(4-Chlorophenyl)-5-(2-furyl)-4-oxazoleacetic Acid (51). Method D. A mixture of **35** (33.1 g, 0.1 mol) and KOH (8.4 g, 0.15 mol) in MeOH (800 mL) and H_2O (100 mL) was stirred at 50 °C for 8 h and was concentrated in vacuo. The residue was diluted with H_2O, acidified with concentrated HCl to pH 2, and then extracted with EtOAc (500 mL × 2). The extract was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated. The residue was crystallized from EtOH to afford colorless needles of **51** (27.6 g, 91%): mp 191–194 °C; IR (Nujol) 1720 cm^{-1}; NMR (Me_2SO-d_6) δ 3.80 (2 H, s), 6.65 (1 H, m), 6.88 (1 H, d, J = 4 Hz), 7.15 and 7.98 (4 H, $A_2'B_2'$, J = 8 Hz), 7.83 (1 H, m); MS, m/z 303 (M^+).

The esters (**33**, **34**, **36–42**, and **44–48**) were similarly saponified. The yields and physicochemical data of the acids obtained (**49**, **50**, **52–62**) are summarized in Table I.

***n*-Heptyl 2-(4-Chlorophenyl)-5-(2-furyl)oxazoleacetate (64). Method E.** To a suspension of **51** (3.0 g, 0.01 mol) in $CHCl_3$ (100 mL) were added $SOCl_2$ (2.6 g, 0.03 mol) and few drops of pyridine. The mixture was stirred at room temperature overnight and then concentrated in vacuo. The residue was dissolved in 1-heptanol (30 mL) and stirred for 5 h. After the reaction was over, the alcohol was removed under reduced pressure, and the remainder was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated. The residue was crystallized from diisopropyl ether to yield colorless needles of **64** (1.52 g, 43%): mp 69–70 °C; IR (Nujol) 3050, 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.55–2.00 (13 H, m), 3.88 (2 H, s), 4.11 (2 H, t, J = 6 Hz), 6.43 (1 H, dd, J = 2 and 4 Hz), 6.62 (1 H, d, J = 4 Hz), 7.34 and 7.92 (4 H, $A_2'B_2'$, J = 8 Hz), 7.41 (1 H, m); MS, m/z 401 and 403 (M^+).

Butyl 2-(4-Chlorophenyl)-5-(2-furyl)oxazoleacetate (65). Method F. A mixture of **51** (3.0 g, 0.01 mol), butyl bromide (2.74 g, 0.02 mol), Et_3N (2.0 g, 0.02 mol), and $CHCl_3$ (50 mL) was refluxed for 10 h. The organic layer was washed with H_2O, concentrated, and chromatographed on a SiO_2 column with a mixed solvent *n*-hexane–EtOAc (1:5) as an eluent. The product was crystallized from diisopropyl ether to yield colorless needles of **65** (2.2 g, 62%): mp 96–97 °C; IR (Nujol) 3050, 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 6 Hz), 1.07–2.00 (4 H, m), 3.94 (2 H, s), 4.17 (2 H, t, J = 6 Hz), 6.56 (1 H, dd, J = 2 and 4 Hz), 6.71 (1 H, d, J = 4 Hz), 7.53 (1 H, m), 7.45 and 8.03 (4 H, $A_2'B_2'$, J = 8 Hz); MS, m/z 359 and 361 (M^+).

Typical Procedure for the Esterification of 51 with CMPI. 3-Pyridylmethyl 2-(4-Chlorophenyl)-5-(2-furyl)oxazoleacetate (67). Method G. To a solution of **51** (3.0 g, 0.01 mol) and CMPI (2.9 g, 0.011 mol) in THF (30 mL) were added Et_3N (2.9 g, 0.026 mol) and nicotinyl alcohol (1.2 g, 0.011 mol) at room temperature. After being stirred overnight, the reaction mixture was poured into H_2O, concentrated, and partitioned between H_2O

and EtOAc. The organic layer was successively washed with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was chromatographed on a SiO_2 column with $CHCl_3$ as an eluent. The product was crystallized from diisopropyl ether to give colorless needles of **67** (1.6 g, 47%): mp 133–134 °C; IR (Nujol) 3100, 1730 cm^{-1}; NMR ($CDCl_3$) δ 3.96 (2 H, s), 5.18 (2 H, s), 6.44 (1 H, dd, J = 2 and 4 Hz), 6.62 (1 H, d, J = 4 Hz), 7.05–8.06 (7 H, m), 8.41–8.68 (2 H, m); MS, m/z 394 and 396 (M^+).

In a similar way, *n*-lauryl 4-oxazoleacetate (**66**) was prepared, and the yield and physicochemical properties are listed in Table I.

Ethyl 2-[2-(4-Chlorophenyl)-5-(3-furyl)-4-oxazolyl]-propionate (70). Sodium hydride (50% on paraffin, 2.4 g, 0.05 mol) was added to a solution of **45** (1.65 g, 0.05 mol) in DMF (30 mL) and THF (30 mL) at −15 °C with stirring. After the formation of reddish brown precipitates of sodium salts of **45**, methyl iodide (0.5 mL, 0.08 mol) was added dropwise at −10 to −20 °C. The mixture was stirred at room temperature for 5 h, concentrated in vacuo, and partitioned between EtOAc and H_2O. The organic layer was washed with H_2O and brine successively, dried with anhydrous $MgSO_4$, concentrated, and then crystallized from EtOH to yield colorless needles of **70** (1.31 g, 73%): mp 108–109 °C; IR (Nujol) 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 1.63 (3 H, d, J = 7 Hz), 3.88 (1 H, q, J = 7 Hz), 4.18 (2 H, q, J = 7 Hz), 6.65–6.85 (1 H, m), 7.38 and 7.97 (2 H each, $A_2'B_2'$, J = 9 Hz), 7.6–7.7 and 7.75–7.8 (1 H each, m); MS, m/z 345 (M^+), 272 (M − COOEt).

Similarly, α-monoalkyl analogues (**69** and **71**) of oxazoleacetates (**35**) were synthesized. The α,α-dimethyl analogue (**72**) was also prepared in a similar manner with excess sodium hydride (3 molar equiv) and methyl iodide (3 molar equiv). The yields and physicochemical data are summarized in Table II.

Typical Procedure for the Saponification of 2-(4-Oxazole)propionates (69 and 72). 2-[2-(4-Chlorophenyl)-5-(2-furyl)-4-oxazolyl]propionate (74). A mixture of **72** (2.0 g, 0.0056 mol) and KOH in MeOH (30 mL) and H_2O (10 mL) was refluxed for 5 h. After removal of the MeOH, the aqueous layer was acidified with 10% HCl to give colorless precipitates of **74** (1.58 g, 86%): mp 186–188 °C; IR (Nujol) 1720 cm^{-1}; NMR (Me_2SO-d_6) δ 1.61 (6 H, s), 6.6–6.9 (2 H, m), 7.52 and 7.98 (2 H each, $A_2'B_2'$, J = 8 Hz), 7.83 (1 H, br s); MS, m/z 331 (M^+), 287 (M − CO_2).

Propionic acid (**73**) was similarly obtained, and the yield and physicochemical data are shown in Table II.

Typical Procedure for the Introduction of an Acyl Group to C-5 of the 5-Furyl Ring of 35. Ethyl 2-(4-Chlorophenyl)-5-(5-acetyl-2-furyl)-4-oxazoleacetate (76). Method H. To a solution of **35** (4.0 g, 0.012 mol) in $CHCl_3$ (50 mL) were successively added acetic anhydride (10.0 mL, 0.1 mol) and boron trifluoride etherate (2.0 mL, 0.015 mol) with ice-cooling, and the mixture was stirred at room temperature for 3 days. The white suspension formed was poured into a mixture of aqueous ammonia and $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by SiO_2 column chromatography with $CHCl_3$–EtOAc (10:1) as an eluent. The crude crystals were recrystallized from EtOH to yield colorless prisms of **76** (2.1 g, 47%): mp 151–152 °C; IR (Nujol) 3100, 1730, 1670, 1490, 1185 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (3 H, t, J = 7 Hz), 2.51 (3 H, s), 3.95 (2 H, s), 4.20 (2 H, q, J = 7 Hz), 7.05 (1 H, d, J = 4 Hz), 7.52 (1 H, d, J = 4 Hz), 7.56 and 7.99 (2 H each, $A_2'B_2'$, J = 9 Hz); MS, m/z 373 (M^+).

Compound **75** was similarly synthesized from **35** (1.0 g, 0.003 mol) by reaction with Vilsmeier–Haack reagent prepared from DMF (5 mL) and $POCl_3$ (3 g, 0.02 mol) at room temperature for 2 days. The same workup of the reaction mixture as described above afforded **75** (0.5 g, 49%): mp 139–140 °C; IR (Nujol) 1710, 1675, 1620, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 1.22 (3 H, t, J = 7 Hz), 3.98 (2 H, s), 4.15 (2 H, q, J = 7 Hz), 7.55 and 8.00 (2 H each, $A_2'B_2'$, J = 9 Hz), 7.16 (1 H, d, J = 4 Hz), 7.66 (1 H, d, J = 4 Hz), 9.63 (1 H, s); MS, m/z 359 (M^+).

Ethyl 5-(5-Bromo-2-furyl)-2-(4-chlorophenyl)oxazoleacetate (77). Bromine (0.93 mL, 0.019 mol) was added to a suspension of powdered NaOAc (4.0 g, 0.049 mol) and **35** (6.0 g, 0.018 mol) in THF (50 mL) and AcOH (50 mL) at −20 to −40 °C. After being stirred at room temperature for 1 h, the reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$ and concentrated. The products were crystallized from EtOH to afford colorless needles of **77** (4.9 g, 66%): mp 120–121 °C; IR (Nujol) 3120, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (3 H, t, J = 7 Hz), 3.97 (2 H, s), 4.25 (2 H, q, J = 7 Hz), 6.45 (1 H, d, J = 4 Hz), 6.66 (1 H, d, J = 4 Hz), 7.43 and 8.00 (2 H each, $A_2'B_2'$, J = 9 Hz); MS, m/z 410 and 412 (M^+).

Ethyl 2-(4-Chlorophenyl)-5-(5-sulfo-2-furyl)-4-oxazoleacetate (78). To a solution of **35** (6.6 g, 0.02 mol) in EtOAc (100 mL) was added H_2SO_4 (3.92 g, 0.04 mol) dropwise at 25–30 °C, and the mixture was stirred for 1 h. The colorless precipitates that formed were collected and partitioned between EtOAc and H_2O. The organic layer was shaken with saturated aqueous $NaHCO_3$ and NaCl. The separate sodium salt (**78**) was treated with 1% HCl and EtOAc. Newly formed colorless precipitates were collected and recrystallized from a mixed solvent of EtOH and H_2O (3:1) to give hygroscopic colorless fine crystals of **78** (3.4 g, 41%): mp 186–187 °C; IR (Nujol) 3400, 1730, 1660, 1600, 1220, 1140, 660 cm^{-1}; NMR (Me_2SO-d_6) δ 1.20 (3 H, t, J = 7 Hz), 3.89 (2 H, s), 4.16 (2 H, q, J = 7 Hz), 6.65 (1 H, d, J = 4 Hz), 6.88 (1 H, d, J = 4 Hz), 7.62 and 8.05 (2 H each, $A_2'B_2'$, J = 9 Hz). Anal. Calcd for $C_{17}H_{14}NO_7SCl \cdot 1.5H_2O$ (438.852): 46.53; H, 3.90; N, 3.19; S, 7.31; Cl, 8.80. Found: C, 46.45; H, 3.72; N, 3.27; S, 7.41; Cl, 8.10.

Ethyl 2-Phenyl-5-(2-tetrahydrofuryl)-4-oxazoleacetate (79). A mixture of **35** (6.6 g, 0.02 mol) and 10% palladium on carbon (1.0 g) in EtOH (200 mL) was shaken with a Paar apparatus under a H_2 atmosphere (4.5 atm) at room temperature for 1 day. After removal of the catalysts, the solvent was removed in vacuo, and the residue was purified by SiO_2 column chromatography with $CHCl_3$ as an eluent to yield a colorless syrup of **79** (2.05 g, 34%): IR (film) 1740, 1180 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (3 H, t, J = 7 Hz), 1.9–2.5 (4 H, m), 3.72 (2 H, s), 3.7–4.4 (2 H, m), 4.21 (2 H, q, J = 7 Hz), 4.9–5.3 (1 H, m), 7.2–7.6 (3 H, m), 7.8–8.2 (2 H, m); MS, m/z 301 (M^+).

Ethyl 3-[(4-Chlorobenzoyl)amino]-4-oxo-4-(1-pyrrolidinyl)butyrate (80). To a solution of **68**[6] (1.2 g, 0.0043 mol) in EtOAc (20 mL) was added pyrrolidine (0.37 g, 0.0052 mol), and the mixture was stirred for 10 min at room temperature. The reaction mixture was washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated. The residue was crystallized from isopropyl ether to afford colorless fine crystals of **80** (1.5 g, 98%): mp 164 °C dec; IR (Nujol) 3270, 1730, 1650, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (3 H, t, J = 7 Hz), 1.6–2.2 (4 H, m), 2.6–3.0 (2 H, m), 3.2–4.0 (4 H, m), 4.10 (2 H, q, J = 7 Hz), 7.29 and 7.75 (2 H each, $A_2'B_2'$, J = 9 Hz); MS, m/z 352 (M^+).

Ethyl 2-(4-Chlorophenyl)-5-(1-pyrrolidinyl)-4-oxazoleacetate (81). A mixture of **80** (3.0 g, 0.085 mol) and PPE (43 g) was stirred for 45 h at room temperature and poured into ice–water (200 mL). After neutralization (pH 7) by addition of aqueous ammonia, the crystals that appeared were collected and recrystallized from isopropyl ether to give colorless fine crystals of **81** (2.71 g, 95%): mp 104 °C; IR (KBr) 3270, 1730, 1650, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (3 H, t, J = 7 Hz), 1.8–2.25 (4 H, m), 3.3–3.6 (4 H, m), 3.63 (2 H, s), 4.30 (2 H, q, J = 7 Hz), 7.31 and 7.79 (2 H each, $A_2'B_2'$, J = 10 Hz); MS, m/z 334 (M^+).

Typical Procedure for the Synthesis of Thiazoleacetates (83 and 84). Ethyl 2-(4-Chlorophenyl)-5-(2-furyl)-4-thiazoleacetate (83). A mixture of **19** (1.75 g, 0.005 mol) and BMDDP[10] (2.80 g, 0.01 mol) in THF (20 mL) was stirred at 50 °C for 6 h. After dilution with EtOAc, the reaction mixture was successively washed with dilute HCl, H_2O, dilute NaOH, and brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was crystallized from EtOH to give colorless needles of **83** (1.5 g, 85%): mp 94–95 °C; IR (Nujol) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 4.04 (2 H, s), 4.22 (2 H, q, J = 7 Hz), 6.49 (1 H, dd, J = 2 and 4 Hz), 6.59 (1 H, d, J = 4 Hz), 7.38 and 7.86 (2 H each, $A_2'B_2'$, J = 9 Hz), 7.49 (1 H, d, J = 2 Hz); MS, m/z 347 (M^+), 274 (M − COOEt).

Similarly, **84** was synthesized in quantitative yield as colorless needles from ethyl 3-[*N*-(4-chlorobenzoyl)amino]-4-oxo-4-thienylbutyrate (**82**):[5] mp 67–68 °C; IR (Nujol) 1735, 1185, 1150 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (3 H, t, J = 7 Hz), 3.90 (2 H, s), 4.22 (2 H,

(10) Davy, H. *J. Chem. Soc., Chem. Commun.* **1982**, 457.

q, J = 7 Hz), 7.23 (1 H, dd, J = 5 and 1.5 Hz), 7.3–7.6 (2 H, m), 7.39 and 7.87 (2 H each, $A_2'B_2'$, J = 9 Hz).

Hypolipidemic Activity in Normal Rats. Male SD rats (4 weeks of age) were purchased from Nihon CLEA Co., Tokyo, and maintained on commercial laboratory chow (Nihon CLEA CE-2 pellets) for at least 1 week before use. Grouping of rats (five rats per group), blood sampling, and calculation of the hypolipidemic effect were performed as described previously.[11] Test compounds were mixed with Nihon CLEA CE-2 powder in a mortar and administrated ad libitum to experimental groups generally for a period of 7 days. The concentration of a test compound in the diet was 50 mg/100 g. Control rats were fed CE-2 powder. On the morning of the 8th day, blood samples were collected from the tail tip under light ether anesthesia, allowed to stand for about 30 min, and centrifuged to yield serum. The serum cholesterol level was measured by the method of Zak et al.[12] or by the enzyme method with Cholestezyme-V "Eiken". Serum triglyceride levels were measured by the method of Ryan and Rasho[13] or by the enzyme method with Triglyzyme-V "Eiken".

The hypolipidemic activity of test compound is expressed in the tables as percent depression of serum lipid levels compared to the control group after the experimental period. The average mean levels of serum cholesterol and triglyceride of the control group in 25 experiments were 84 ± 1 and 79 ± 3 mg/100 mL, respectively. Clofibrate, used as a positive control drug, reduced serum cholesterol and triglyceride by 15 ± 1% and 30 ± 2% (N = 33), respectively, under these conditions.

Hypolipidemic Activity in Hereditary Hyperlipidemic Rats (THLR/1).[8] One of the active compounds (**35**) was examined in hereditary hyperlipidemic rats (THLR/1),[8] which were produced by in-breeding and maintained at our research laboratories. Four week old male rats and 5–7 week old female rats were used. Compound **35** or clofibrate was administrated to rats in various concentrations between 0.001% and 0.02% in the diet for 7 days. On the morning of the 8th day, serum cholesterol levels were measured by the methods described in the above section. Percent decreases in the serum lipid levels were calculated from the values before and after drug administration.

Inhibitory Effect on Collagen-Induced Platelet Aggregation (in Vitro). Blood was withdrawn from the abdominal aorta of male SD rats (250–300 g, purchased from Shizuoka Laboratory Animals Corp.) under ether anesthesia. The blood was mixed with a one-tenth volume of 3.8% trisodium citrate and centrifuged at 500g for 10 min. The upper layer was used as platelet-rich plasma (PRP). The bottom layer was further centrifuged (1000g for 10 min) to give platelet-poor plasma (PPP). The platelet content of PRP was adjusted to (8 – 10) × 10^5 cells/mm^3 of plasma by dilution with PPP. Platelet aggregation was measured at 37 °C by the method of Born[14] in a NKK aggregometer (PAT-4A) and expressed as percent of the difference in absorbance between PRP and PPP. To 200 μL of PRP was added 25 μL of test sample solution (final concentration: 100 μg/mL) in a cell, and the mixture was stirred at 37 °C for 2 min. Aggregation was induced by adding 25 μL of collagen suspension (25 μg/mL of reaction mixture). Collagen suspension was prepared from collagen of bovine Achilles tendon (Type I, Sigma) by the method of Holmsen et al.[15] Inhibitions of platelet aggregation were calculated by the following equation:

inhibition of platelet aggregation =
[1 – (degree of platelet aggregation with test agent)/(degree of platelet aggregation without test agent)] × 100

The inhibitory effect of test compound was expressed as (–) if the percent inhibition is less than 10%, (+) if the inhibition is equal to or above 10% but less than the inhibition (34–96%) concurrently obtained with aspirin (100 μg/mL), and (++) if the inhibition is equal to or above the inhibition by aspirin. The results are tabulated in Table I and II.

Effect of Oral Administration of 35 on Collagen-Induced Platelet Aggregation in Hyperlipidemic Rats (ex Vivo). Male SD rats (weighing 250–300 g, 6 weeks old, seven animals per group) in group 1 (control I) were fed only the CE-2 basal diet throughout a 29-day experimental period. Rats in the other two groups were allowed free access to a cholesterol-rich diet made by adding 1% cholesterol, 0.2% sodium cholate, and 5% olive oil to the basal diet and water containing 0.02% 6-propyl-2-thiouracil throughout the experimental period. Rats in group 2 (control II) were given orally (10 mL/day) of Nikkol CHO-60 (Nikko Chemicals)–(carboxymethyl)cellulose solution alone during the administration period from the 15th to 29th day of the experimental period. Rats in group 3 were administered orally (100 mg/kg per day) **35** dissolved in 10 mL (per kilogram of body weight) of Nikkol CHO-60–(carboxymethyl)cellulose solution from the 15th through 29th day.

One hour after administration of the testing agent on the 29th day, blood was collected from the abdominal aorta under ether anesthesia. To 4.5 mL of the blood was added 0.5 mL of 3.8% trisodium citrate, and the mixture was centrifuged at 250g for 5 min. PRP and PPP were prepared as described above. Platelet aggregation was induced with collagen (7 μg/mL of reaction mixture) as described above. This amount of collagen did not induce aggregation of the platelets from the rats fed the basal diet but did induce aggregation by 28 ± 9% with the platelets from the rats fed the hyperlipidemic diet.

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